Career pathways, part 10

Christiane D. Wrann and Jin Zhang

In our tenth instalment of Career pathways, Jin Zhang and Christiane Wrann reflect on their journeys to becoming PIs and the importance of having a vision for your research, finding the right team, and sharing the joy of science through the training of students.

Jin Zhang: an entrepreneurial journey

I became intrigued by science from an early age because my mother, a middle school biology teacher, brought science books home when I was a child. Later, I chose to study cellular and molecular biology because my interest was sparked when I was in graduate school at UCLA working on stem cell metabolism, and was further trained at Harvard Medical School on metabolic regulation of stem cell reprogramming. I sort of grew alongside the stem cell metabolism field. In its infancy around 15 years ago, with the excitement of induced pluripotent stem cells (iPSCs) and the curiosity about how similar they are to embryonic stem cells (ESCs), a number of groups including my PhD lab studied the very fundamental aspects of stem cell metabolism, and the journal *Science* highlighted 'stem cell metabolism' in their special column of 'Areas to watch' in 2012. In the next decade, metabolism studies in cancer, immune cells and stem cells in parallel continued to flourish.

When I established my own lab in 2017, I was determined to continue in this direction, but had a feeling that studying stem cells only in vitro would inevitably miss important contexts of the physiological developmental environment, particularly for mammalian embryonic stem cells that reside in pre-implantation embryos. However, it was intimidating to harvest tens of thousands of embryos to perform experiments such as mass spectrometry, which is a common way to study metabolism in other contexts. It was not until we assembled a team comprising a great embryologist, Jing Zhao (who was also the first graduate student in my lab), a fantastic bioinformatician, Hua Yu (who was my first postdoc), and a great biochemist and collaborator, Zeping Hu (who had rich experience in mass spectrometry) that we could seriously start to depict the metabolic landscape of mammalian pre-implantation embryo development.

Just like in any newly started lab, this was a pivotal project that required tons of work to build the system from scratch, and, if successful, would help our young laboratory to become established in a new field. Thus, this project means a lot to us. It was a struggle at the beginning owing to the technical challenges of handling low-input samples, and I had to constantly encourage the student by saying "a hard project at the beginning might end up easier in the end, because by overcoming the great challenges, you build your competitive edge and that makes it harder for other groups to catch up." Eventually, we managed to reduce the amount of material needed from an astounding number (tens of thousands) of embryos to a dozen embryos through a targeted metabolomics approach. In the end, when the paper was finally published in *Nature Metabolism* (Zhao et al., https://doi.org/10.1038/s42255-021-00464-x), we were so thrilled to be able to share the metabolic programs of mouse pre-implantation embryos with our colleagues in the fields of metabolism, developmental biology and stem cell biology. The paper received great feedback as groups from around the world contacted us for a copy. The paper has also brought us immediate opportunities; for instance, both my trainees and I have received a couple of grants from the National Natural Science Foundation of China owing to this paper. We have also received invitations to write review articles on 'metabolism in development' for prestigious journals. My graduate student eventually secured a faculty position at a great institute in China mainly because of this study, which sparked her persistent interest and strong passion in this emerging field of developmental metabolism.

We are on an ongoing scientific journey, as there are still plenty of opportunities for technical improvement, and many unknown 'developmental metabolites' in various developmental stages, in different cell and tissue types during development, and even in different species. It opens up such a horizon for us not only in research but also in its clinical impact. Quite a few doctors from the obstetrics and gynaecology departments of hospitals or IVF clinics have contacted us to exchange their thoughts about the nutritional state of in vitro fertilized and cultured human embryos after they came across our paper.

Looking back at the past five years when I was on the road to establishing my own lab, it was to some extent a very entrepreneurial journey where building a team is at the core. I would not have had the same productivity without the bioinformatician and the embryologist on board. It is not hard to find a student to just follow your guidance, but it is much more difficult to find a team member that can complement your expertise. It took me a lot of time and advertising effort and a bit of luck to assemble the team. In our team, instead of a unidirectional output from me, we worked together by mutually contributing to each other's expertise and ideas. While I spent plenty of time teaching the lab members what I know about stem cells and metabolism, one of the key roles I played was to identify the key scientific questions and to put together our story to best answer that question. Now these trainees have become truly knowledgeable experts in this field and I am more than satisfied with their progress in both science and career development.

In addition to team building, funding is a top priority for a new PI. In a top institute such as Zhejiang University in China, we have a generous startup package for the first few years. However, it becomes more and more competitive to secure a grant from the National Natural Science Foundation, and the funding rate for a regular grant has become as low as 10–20%. We need to constantly keep alert for new grant opportunities and sometimes organize teams to apply. On this topic, our university did a great job in providing all kinds of information and tutoring for new PIs.

As for some tips for early career students or postdocs, one important thing is to know what you want to pursue as early as possible. My first graduate student came as an embryologist after working in an IVF lab in a hospital for seven years. She had encountered many mysteries in the IVF procedures that could not

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be answered either by herself or sometimes by her mentor. She joined graduate school and was able to maintain that interest and curiosity. When she graduated, she could return to the IVF lab or stay in academia, and she chose the latter because she knew she was interested in doing research to answer those questions raised during the clinical practice of embryo development in a culture dish or during her studies of embryo development in utero.

Another tip is to give trainees a continuous source of achievements, such as publishing some protocols or review articles before the big primary research paper, securing grants, and presenting at conferences. It takes a long time to wrap up a complete story and push it to be published in a top journal, and along that way continuous motivation and interest need to be reinforced by positive feedback, no matter how small. For instance, I would arrange for a junior trainee to write a methods paper or a review article, and once the students have these pieces of work published at the beginning of their academic career, it serves as important further encouragement. The same is true for a young investigator grant, or a presentation at a local conference. I benefited from these in my own graduate study at UCLA, and I passed it along to my own trainees.

In a nutshell, I think being a young PI is such a fantastic experience for me. Being excited by the pure science and by watching trainees grow are definitely the best parts of it. Beyond that, I also cherish the entrepreneurial spirit throughout the life of being a PI. This includes building a team, looking for the most promising directions with your instinct and judgement, facing setbacks and ploughing through every detailed task to execute your plan. I used to have an interesting discussion with my postdoc mentor by asking: "what is it like to pursue entrepreneurship as a career opportunity?" And the answer was: "everyone in academia is an entrepreneur at heart." Another career mentor of mine also set a great example of what he called 'academic entrepreneurship' in that a PI not only pursues highly innovative research in the lab, but also translates some of the research into a real venture outside the lab.

As a PI or any early career investigator, a work–life balance can also be a privilege. The conventional idea is that it takes 120% of your time to be a PI. However, this doesn't necessarily mean spending lengthy hours in the office, but rather having the mindset that you have to push yourself to reach the highest level possible. I spend lots of time thinking hard about science while being out of the office, and in the meantime, I gain plenty of flexible hours to be physically outside of my office and have a balanced life with my family. In my leisure time, I enjoy traveling with my wife and my 7-year-old daughter on weekends or holidays, to just completely refresh myself.

Christiane D. Wrann: have a vision

I started my career in biomedical sciences by pursuing a Doctorate in Veterinary Medicine (DVM) at the University of Veterinary Medicine in Hannover, Germany. Veterinary medicine, or comparative medicine as it is now more aptly called, provides excellent training for a research career. It combines a rigorous curriculum in the basic sciences with pathology and pharmacology across many different species, encouraging critical thinking early on. Halfway through my training, I realized I was very interested in solving a 'medical mystery' and finding the correct diagnosis. Yet the daily routine of clinical care was not as exciting as I had expected. I distinctly remember a day when we had to explain the exact same diagnosis and treatment to three separate clients. My first mentor, Christine 'Nina' Becker, an equine surgeon from Hamburg with a PhD, recommended I consider research to challenge my curious mind – a suggestion that completely changed my career trajectory. I applied for and won scholarships to attend summer school research programs for DVM students at the University of Cambridge, UK, and Cornell University. Hooked by the excitement of discovery and the potential to see or create things no one else had before, I decided to pursue a PhD in Immunology, also in Hannover.

Under the mentorship of Niels Riedeman and Heike Kielstein, I investigated the regulation of C5a-mediated effects on innate immune functions during experimental sepsis and graduated Summa cum Laude. Dr Riedeman emphasized the effects biomedical research can have on the lives of many if the findings can be translated into the clinic. Dr Kielstein encouraged me to stretch myself to dream bigger and pursue postdoctoral training abroad in the United States to be exposed to cutting-edge science. She also encouraged me to apply for a DFG (the German NIH equivalent) fellowship. A note to young (female or minority) scientists: I was told many times in my career that certain things (scholarships, positions, or projects) are only for the "really good people but not you." Ignore these voices and find mentors or networks that support you. With a DFG travel fellowship, I went to Boston for what was supposed to be a six-month-long exchange experience to work in Evan Rosen's lab at Beth Israel Deaconess Medical Center/ Harvard Medical School on transcriptional regulation in adipocyte-specific leptin gene expression. However, the exciting project, combined with Evan's excellent mentorship and the unique scientific environment, made me stay on. Evan was the first to bring up the possibility of me becoming faculty at (what he called) a 'cutting-edge science institution' in the United States and suggested a second postdoc to strengthen my competitiveness. We published a beautiful tour-de-force paper together[1], and now, ten years later, I am still in Boston with a family, a house, and a faculty position at Massachusetts General Hospital/ Harvard Medical School.

I started working on the neuroprotective effects of exercise as a postdoctoral fellow in Bruce Spiegelman's laboratory at Dana-Farber Cancer Institute/Harvard Medical School. Bruce had a great reputation for doing very mechanistic studies on exciting new biology, including on exercise, and was well known for his outstanding mentoring track record. Both promises were true: the science was exhilarating, and Bruce's mentorship was exceptional. In his lab, I focused on the role of the newly discovered exercise hormone FNDC5 and its secreted form irisin. I identified a novel PGC1a–FNDC5–BDNF pathway in the hippocampus that is induced by endurance exercise and, in part, mediates the positive effects of exercise in the brain[2]. Follow-up work described a quantitative mass spectrometry-based assay, which has become the gold standard in the field, to measure circulating irisin in humans[3].

For the academic job search, I followed the classic formula of publishing a 'big paper', then a follow-up paper, and getting a K Award – in my case, a K99/R00 from the National Institute of Neurological Disorders and Stroke. I was invited for several interviews and received several job offers, from which I chose the position at Massachusetts General Hospital/ Harvard Medical School, as it was the best fit. Since my predecessors in the Career pathways series have covered environment, fit and mentors as critical aspects of the job search, I will focus on negotiation advice. Negotiate well, but in good faith, as these will be your colleagues for years to come. If you decide not to accept an offer, let them know straight away. Ask only for

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what you require, but also make sure you have everything that you need. As they say, once the ink is dry, that is it. Ensure that the equipment and infrastructure meet all your current needs and allow your research program to grow. For salaries and start-up packages, try to get real numbers by talking to mentors and fellow postdocs who recently started their labs. Remember to compare apples to apples: some offers will include your salary in the start-up package, and some keep it separate. Research expenses, such as salaries, core services and animal per diem costs, vary significantly by location, so the same start-up funds have very different buying power in high-cost versus low-cost areas. Last, keep in mind that what makes the best offer is not just the highest number, but the one that will give you the best position to start your lab and build your research program.

When establishing your own lab, the most important thing is to have a big vision for your science, for two reasons. First, as long as you maintain your big goal, even if you fail in this goal, you will achieve something good. Second, only a big dream will give you the necessary boost to persevere in the face of adversity. My mentor Bruce Spiegelman gave me another excellent piece of advice: "Do great science first, then the rest will follow." He was absolutely right. However, this can be hard to remember when in the thick of it of it because it takes a lot of time and effort to get to that point. My lab reached a critical milestone when our first big paper was published recently in *Nature Metabolism* (Islam et al., https://doi.org/10.1038/s42255-021-00438-z). As discussed above, during my postdoc with Dr Spiegelman I investigated the FNDC5/irisin pathway in exercise, but an important open question remained: whether irisin was the active moiety conferring the cognitive benefits of exercise. From the translational point of view of a biotechnologist, working with FNDC5 (a larger type I membrane protein) is far more challenging than working with irisin, a small natural peptide hormone that is 100% conserved between mouse and human. Therefore, my lab drilled down into that question and identified the myokine irisin as a crucial regulator of exercise's cognitive benefits and a possible therapeutic target for Alzheimer's disease in preclinical models, in part by reducing neuroinflammation. Our study in *Nature Metabolism* was nicely covered by popular news outlets such as the *New York Times* and *National Geographic*. On the basis of data published in the paper, I received my first R01 and the ADDF Harrington Scholar Award, which allows my lab to further investigate irisin's mechanism of action and perform more translational studies towards developing irisin as a drug for dementia. Many invitations to speak nationally and internationally about this study have led to other exciting collaborations and projects.

The biggest challenge to publishing our first 'big paper' was the time it took to finish the project, because, first, I had a child, and then the COVID-19 pandemic disrupted everything. Over time, several trainees had come and gone. While labs were (partially) shut down, we had to get creative to complete experiments. For example, we outsourced RNA extraction and RNA sequencing to a company instead of academic cores, which were either temporarily closed or had a considerable backlog. Instead of doing the microscopy ourselves, we used a slide scanner. Most important during this time, though, was the willingness of the people in my lab to work together as a team and their determination to get the project across the finish line.

One area where I have found unexpected joy is in training the next generation of scholars. I am particularly interested in supporting the careers of women and underrepresented-in-medicine (URM) individuals, as reflected by the above-average number of female and URM trainees in my lab. I have built a strong connection with the co-op program at Northeastern University, which has a much higher percentage of URM students than other Boston-based institutions. I also serve on a committee to improve diversity, inclusion and equity at Massachusetts General Hospital. I am very proud of my trainees' achievements. One of my recent URM trainees was a finalist for the Rhodes Scholarship. Others I have had the privilege to mentor have graduated from medical school or started postdoctoral training in their dream lab. I know all these young people will go on to achieve admirable things, and it feels great to have been a part of their path.

One of the major privileges of being an academic PI is the ability to pursue your passion – as long as you have adequate grant funding. I enjoy many aspects of my job: the thrill of discovery, giving talks, writing papers, stimulating interactions with other scientists. Indeed, many parts of my job energize me. However, being a PI at a 100% soft-money institution comes with particular challenges. People, including me, will not get paid without securing sufficient funding. In addition, one must raise more funds to cover 100% of one's salary, which means more time spent on grant writing. When starting a lab, the buck always stops at the PI. In addition, ever-increasing regulatory burdens take time away from actual research.

Amidst these pressures, family time and quality time with my daughter are important ways to ground myself and remember that there are more important things in life than a rejected paper or unfunded grant. As an exercise scientist, I would again emphasize exercise's role in overall well-being and health. I personally enjoy the great hiking in New England and yoga. As a working mom, the overall hours are a lot, but the flexibility of academia is a huge plus. Overall, academic freedom, intellectually satisfying work, and the chance to have important impact on others' lives make being an academic PI a great career choice.

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References

1. Wrann, C. D. et al. *J. Clin. Invest.* **122**, 1010–1021 (2012).
2. Wrann, C. D. et al. *Cell Metab.* **18**, 649–659 (2013).
3. Jedrychowski, M. P. et al. *Cell Metab.* **22**, 734–740 (2015).